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CORPORATION

Lilia Talarico, M.D.
Director, Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room 6B-30
5600 Fischers Lane
Rockville, MD 20857

IND 25,512: Emitasol® (Metoclopramide) Nasal Spray
S-106: General Correspondence

Dear Dr. Talarico:

Reference is made to our IND for Emitasol Nasal Spray, cited above, and to our End-of-Phase II Meeting held

The purpose of this letter is to provide you with a copy of our summary of the meeting. We would appreciate receiving a copy of your summary of the meeting as soon as it has been issued. Kindly address the summary to my attention at:

Roberts Pharmaceuticals
4 Industrial Way West
Eatontown, NJ 07724-2274

Should you have any questions regarding this submission, please contact me at your earliest convenience. My telephone number and Fax numbers at Roberts are (732) 676-1270 and (732) 676-1300, respectively.

Sincerely,

David Haenick

David Haenick, Ph.D.
Senior Manager
Regulatory Affairs

Encl.

Emitasol (Metoclopramide) End-of-Phase II Meeting

The Emitasol End-of-Phase II meeting was held in the Chesapeake Room of FDA's Parklawn Building. The attendees were as follows:

Roberts: Dr. M. Petrone, Mr. A. Howard, Dr. E. Yau, Dr. D. Haenick

Ribogene: Dr. L. Lehman, Mr. F. Sasinowski

GloboMax: Ms. J. Chiostri, Dr. E. Heyman, Dr. R. Oliver, Dr. C. Trapnell

Consultant: Dr. J. Gilden

FDA: Ms. M. McNeil, Dr. L. Talarico, Dr. H. Gallo-Torres, Dr. J.B. Choudary, Dr. E. Duffy, Dr. J. Hunt, Dr. S. Al-Fayoumi, Dr. A.J. Sankoh

The meeting was conducted according to a question-answer format. The FDA presented a formal written response to each question that was submitted in advance by Roberts. The meeting began at 3:00 PM and concluded at 4:30 PM.

Question #1: We propose to conduct two new 3-month subacute local tolerability studies in rabbits and monkeys. Histopathologic exams will be limited to the upper respiratory system and the upper gastrointestinal system only. Two previous studies conducted for 14-28 days in rabbits and monkeys also will be submitted. Other pharmacology and toxicology data will be obtained from the literature for studies conducted for the metoclopramide products currently available. Is this acceptable to the agency?

Response:

Question #2: Human pharmacokinetic data for the bioavailability of metoclopramide nasal spray as compared to oral and intravenous metoclopramide will be submitted from studies conducted previously in healthy human volunteers. Is this acceptable to the agency?

Response:

Question #3: Metoclopramide is an old drug with a well-known safety profile. The oral tablet is indicated for the treatment of diabetic gastroparesis. Therefore, we propose to conduct one randomized, double-blind, double-dummy, positive controlled clinical study in patients with diabetic gastoparesis comparing the metoclopramide 10 mg orally before meals and at bedtime (the approved dose for this indication) to metoclopramide nasal spray at a dose that gives comparable systemic metoclopramide. Primary endpoints include improvement from baseline in the assessment of subjective symptoms and quality of life. A secondary endpoint would be comparison of gastric emptying time at study completion from the baseline assessment. The study would also include a population pharmacokinetic/pharmacodynamic analysis to explore these relationships. Is this acceptable to the agency?

Response:

Question #4: We believe the double-blind, double-dummy design of the above mentioned clinical trial is critical to the outcome of the study given the subjective endpoints that will be assessed. However, the product identification markings on all approved metoclopramide oral tablets will require encapsulation of the metoclopramide active and placebo tablets in order to maintain the study blind. We propose to establish the bioequivalence of encapsulated versus unencapsulated metoclopramide tablets using *in vitro* dissolution testing. Is this acceptable to the agency?

Response:

Question #5: We hope to show in the proposed pivotal trial that the metoclopramide nasal spray will be noninferior to oral metoclopramide tablets for the treatment of the symptoms of diabetic gastroparesis. Our statistical analysis plan will be based on the results of a three-week, double blind. placebo-controlled, study in 34 patients with delayed gastric emptying which compared oral metoclopramide 10 mg four times daily to placebo. The primary response variable was the sum of the following nine subjective questions, each graded on a five-point scale (0 = none, 1 = slight, 2 = moderate, 3 = marked, and 4 = extreme):

1. Early satiety
2. Postprandial bloating
3. Nausea
4. Vomiting
5. Meal Tolerance
6. Epigastric pain
7. Heartburn
8. Belching and regurgitation
9. Anorexia

Baseline mean scores were 18.3 and 18.4 for patients in the metoclopramide and placebo treatment groups, respectively. The mean change from baseline in the total score among patients treated with metoclopramide was 8.9, and among patients treated with placebo was 4.1. The mean drug effect (change from baseline on active drug minus that on placebo) was 4.8. We propose that 50% of the mean drug effect (2.4) observed in this study be used as the delta in a test of noninferiority between metoclopramide nasal spray and metoclopramide oral tablets. Therefore, the formal statistical test will be that metoclopramide nasal spray is not more than 2.4 points worse metoclopramide oral tablets, based on the above scale. Is this acceptable to the agency?

Response: